

Best Antibiotics for Buccal Delivery

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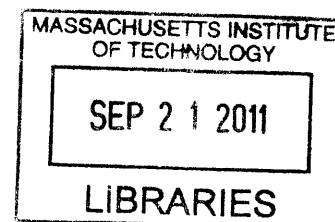
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by
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Abstract

Purpose

The purpose of the research was to identify the clinical and commercial benefits of switching from intravenous (IV) to buccal delivery of antibiotics. then, the research continued to select 3-5 antibiotics that best met the buccal delivery and market requirements.

Methods:

The research began with the hypothesis that some injectable antibiotics are good candidates for buccal delivery even with the limitations imposed by the buccal tissue. The thesis captures a two-year research period encompassing three critical fronts – the clinical viability of switching from IV to buccal delivery for antibiotics, the market's desire and readiness to switch, and the antibiotic brands available for commercialization. Then the research moved to drug identification and selection in order to assess the antibiotics that would best function in the buccal delivery model.

Results:

Intravenous (IV) antibiotics are usually reserved for severe infections that require faster treatment. Less aggressive bacterial growths are treated with oral antibiotics, which has fewer side effects and complications. In the past two decades, the understanding of drug transport across different tissues has increased resulting in improved patient adherence to the therapeutic regimen and pharmacologic response. The administration of drugs by transdermal or transmucosal routes are relatively painless, offers patients more choices, and reduces the need to establish intravenous access, which is a particular benefit for children and elderly. These alternative methods also provide clinical care providers with more choices to better manage their patient's course of treatment. In the past, clinicians administered sedatives, narcotics, and a variety of other medications by transdermal, sublingual, nasal, rectal, and even tracheal-mucosal

routes. These delivery options have provided flexible practice settings and this paper intends to show that antibiotics could be the next set of drugs to be administered in variety of ways to provide patients and clinicians the best array of choices.

Conclusion:

A few years ago, the buccal delivery method was fairly unknown. However, advances in nano encapsulation, physiology, toxicity, and the availability of certain drugs make the timing ideal for introducing antibiotics that have undergone a highly selective process for delivering through the buccal tissue.

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I especially want to thank my wonderful husband, Peter Goldberg, my children Sonya and Eric, my mother Mansoureh Tajallai and my sisters Firoozeh and Fereshteh Nazari for all the years of constant love and encouragement. I like to express my lasting gratitude to my best friend, Sandra St. Fleur for supporting me unconditionally, helping me with edits, sorting through the data and untangling the mysteries of drug delivery.

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Chapter 1: Introduction

Intravenous (IV) antibiotics are usually reserved for severe infections, which require faster treatment. Lesser bacterial growths are treated using oral antibiotics, which carry fewer side effects and chances for complications. The risks associated with the use of IV antibiotics, including the development of drug-resistant bacteria, make it necessary for clinical care givers to restrict their use.

According to “General Standards of IV Therapy” guide, if the patient is suffering from a non-life threatening illness, the benefits of using IV methods of treatment versus oral medication should be weighed against the potential serious side effects. Furthermore, the guide stipulates the need to explain to the patient the risks and benefits inherent in the two methods for delivering antibiotics so that the patient is able to make and decision ^[5]. This thesis focuses on the possibility of using oral antibiotics as the preferred method of delivery due to the apparent benefits of risk reduction and patient’s well being.

In the past two decades, the understanding of drug transport across different tissues has increased resulting in improved patient adherence to the therapeutic regimen and pharmacologic response. The administration of drugs by transdermal or transmucosal routes are relatively painless and provides patients with ease of use, and reduces the need for intravenous access, which is of particularly benefit for children and the elderly ^[3]. These alternative methods also provide practitioners more choices to better manage their patient’s course of treatment ^[5].

Historically, clinicians have administered sedatives, narcotics, and a variety of other medications via transdermal, sublingual, nasal, rectal, and even tracheal-mucosal routes thereby effectively increasing delivery options and increasing both patient and clinician choice ^[19] . This paper intends to demonstrate that antibiotics can become the next set of drugs to be administered in variety of ways and provide patients and clinicians with a similar array of choices. The ultimate aim of this thesis paper is to investigate the possibility of creating patient-friendly antibiotic buccal patches to substantially improve patient compliance, reduce hospital stay, and significantly decrease the devastation and health care costs of medical complications due to hospital associated infections (HAIs). This paper's primary focus is the delivery of certain antibiotics in buccal patches, where it is believed they will have immediate and lasting positive impact given the current therapeutic landscape. This investigation is the first step toward research and development of an effective, safe medicated buccal patch that can easily be shipped anywhere in the world, is simple to use, easy to understand dosing, convenient to carry, does not require refrigeration and has a long shelf life. The patch can help millions of patients around the globe who fear needles or have limited access to clinics, needles, and refrigeration.

This paper provides guidelines and criteria for the selection of antibiotic candidate drugs. Some of these requirements are based on the mechanical and biochemical properties of the physical delivery device, which in this case is the buccal patch. The properties include: 1. The efficacy of release triggers such as the biochemical properties of the saliva, mouth pH and optimal release of the antibiotic within the nano particles. 2.

The interdisciplinary aspects of the mechanical capacity and biological attributes of the nanoparticles to contain the required amount of drugs. 3. Effect of environmental variables such as humidity, light, and temperature on the mechanical and biochemical integrity of the nano particles, the drugs, and base materials used in the dissolvable. 4. The mechanical and biological impact of the permeation enhancers on the oral cells as well as the fat and muscle cells. 5. The time needed to effectively release the specified amount of the drug and meet the medical bioavailability requirements.

The findings reflected in this thesis are based on two years of academic, clinical, and market research. The academic component of the research focused on better understanding the impact of the buccal delivery method of human physiology when compared to the IV delivery methods. The market research component focused on the benefit to patients, physicians, and hospitals. The marketing component focused on antibiotics currently on the market that fit the standards established for antibiotics that can be used in the buccal delivery method. The conclusions of the research so far lead the author to believe that the buccal delivery system presents lower risks to patients, is more cost effective for hospitals, and can be used with some highly selected antibiotics currently on the market that fit the criteria established by the research protocol.

The following diagram illustrates the various action steps in the research process. It also describes the relationships among the steps.

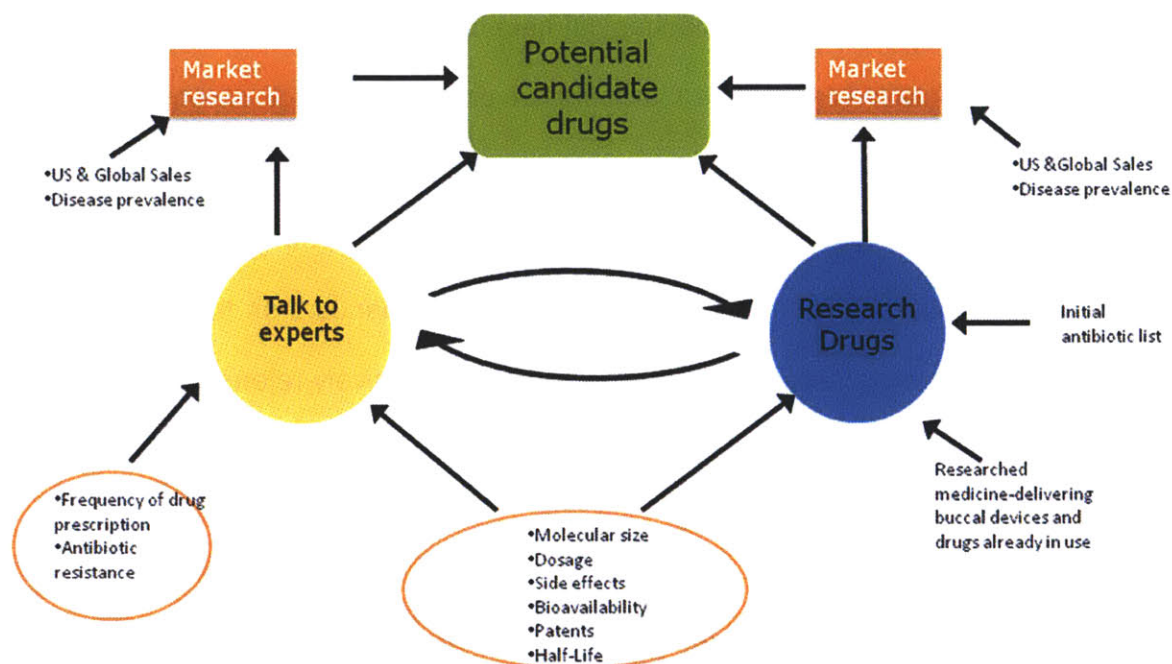


Figure 1: The Strategies used to complete this thesis

The thesis is organized in the following manner:

- **Chapter 2:** General Overview of Buccal Delivery and Antibiotics

Chapter 2 covers why buccal delivery is an attractive drug delivery choice to researchers and pharmaceutical companies. It also gives an overview on antibiotics, bacteria resistance and what class of antibiotics is the focus of this thesis.

- **Chapter 3:** General Side Effects of IV therapy

Chapter 3 covers the infections associated with IV therapy and contamination of the catheter hub that contribute substantially to intraluminal colonization of long-term catheters. It explains the training that is required by the clinicians to reduce infection risks caused by injection.

- **Chapter 4:** Mucosa Membrane

Chapter 4 describes the properties of mucosa membrane and then focuses on the buccal mucosa and administration of drugs via this membrane to the systemic circulation. It covers the anatomy and physiology of oral mucosa and help the reader understand why the buccal region can be a used for drug delivery.

- **Chapter 5:** In-depth analysis of Buccal Drug Delivery

Chapter 5 describes the concepts and compounds used to increase the efficacy of the buccal mucosa. It discusses how mucoadhesive polymers and permeation enhancers can be useful in making buccal delivery a viable alternative to oral and IV delivery techniques. It also describes the advantages and disadvantages of the buccal delivery methods.

- **Chapter 6:** Buccal Delivery Drugs and Patches

This chapter focuses on the drug characteristics that are important for buccal drug delivery. It also exhibits the known formulations used for increasing bioavailability and lists FDA approved drugs that are currently delivered via this method. Finally it covers the design of buccal patches that are well suited for drug delivery.

- **Chapter 7:** Antibiotic Marketing and Business Requirements

This chapter discusses the key marketing and business elements for successful commercialization of buccal antibiotics. It discusses why buccal delivery is an effective response to clinical needs based on research by CDC and Frost and Sullivan's reports.

- **Chapter 8:** Requirements for this research

This chapter covers the business, scientific and clinical considerations of this research. It also lists the buccal delivery considerations that we used in this research to help narrow down the selection of suitable antibiotics. There is a table in this chapter that

shows some of the antibiotics that were investigated and the elements that were used to eliminate some for buccal patch delivery.

- **Chapter 9: Final Drug Candidates**

This chapter covers the 4 antibiotics and one osteoporosis drug that meets the research requirements of this thesis.

- **Concluding Remarks**

- **References**

- **Appendices:** Additional information that exhibits how we conducted the research and made some of our conclusions.

Chapter 2: General Overview of Buccal Delivery and Antibiotics

Why Buccal Delivery?

The most commonly employed route for the administration of medications is the peroral route but, due to the limitations associated with the peroral route such as extensive first-pass metabolism and hydrolysis of acid-labile drugs, the potential use of other routes of drug administration such as the buccal need to be investigated^[7].

Drug delivery forms such as tablets, gels, solutions, and patches can be placed in the buccal pouch^[31]. Modifications can be made to the buccal tissue's permeability or to the local environment of the mouth to allow absorption of the active drug into the blood circulation. Drug delivery via the buccal mucosa is rapidly emerging due to the fact that this route of delivery possesses many advantages over the other routes, which involve extensive first-pass metabolism. Even compared to the other mucosal and transdermal routes of delivery, the buccal mucosa appears to be better in terms of permeability, surface area, patient compliance. Another advantage of the buccal mucosa is that it is more resistant to tissue damage and irritation since it is frequently exposed to different types of food with variety of pH levels. Its cell turnover, when compared to other mucosal routes of administration, is also very rapid, which makes it heal quickly. Hence the buccal route of delivery is the logical alternative delivery route for drugs which, if delivered orally undergo extensive degradation in the stomach and liver^[7,8].

Overview of Antibiotics

“The first rule of antibiotics is to try not to use them, and the second rule is try to not to use too many of them” ^[33].

—Paul L. Marino, *The ICU Book*

An antibiotic is used synonymously with antibacterial and is a compound that kills or slows down the growth of bacteria ^[12]. With the increased understanding of infectious diseases, the definition of antibiotic has been broadened to include antimicrobial compounds, anti-fungal and other compounds ^[13].

In 1942, Selman Waksman defined “antibiotic” as a substance created by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. This definition excluded substances such as gastric juices and hydrogen peroxide that kill bacteria but are not produced by microorganisms. The definition also excluded compounds such as sulfonamides, which are synthetic antibacterial. Many antibacterial compounds are relatively small molecules with a molecular weight of less than 2000 atomic mass units ^[13].

With advances in medicinal chemistry, most of today's antibiotics are semi-synthetically created by modifying natural compounds. For example, beta-lactam antibacterials include the penicillin, the cephalosporins, and the carbapenems. Compounds that are still isolated from living organisms are the amino glycosides, whereas other antibacterials such as the sulfonamides, the quinolones, and the oxazolidinones, are produced solely by chemical synthesis ^[14]. Accordingly, many antibacterial compounds are classified on the basis of chemical/biosynthetic origin into natural, semi synthetic,

and synthetic. Another classification uses antibiotics biological activity; which are divided into two broad groups based on their biological effect on microorganisms: bactericidal agents kill bacteria, and bacteriostatic agents slow down or stall bacterial growth ^[14].

In this thesis, the focus is on broad-spectrum antibiotics since they are more widely used in current clinical settings. The term broad-spectrum antibiotic refers to an antibiotic that acts against a wide range of disease-causing bacteria. A broad-spectrum antibiotic such as ampicillin fights both Gram-positive and Gram-negative bacteria, which is unlike the narrow-spectrum antibiotic, which works against a specific family of bacteria ^[34].

This thesis also considers issues associated with bacterial resistance, which can be magnified if bioavailability of the antibiotic is poor. The striking, widespread increase in bacterial resistance to antibiotics is an issue of great concern. Worldwide emergence of antibiotic resistance in common gram-positive coccal pathogens is probably the most devastating issue in the bacterial infection landscape. The most important of these organisms are penicillin-resistant *Streptococcus pneumonia*, vancomycin-resistant *Enterococcus*, and methicillin- (and now vancomycin-) resistant *Staphylococcus aureus*. Although known by the above names, all of these organisms are multidrug-resistant. Beta-lactam and vancomycin resistances in gram-positive cocci are caused by altered cell wall binding sites with decreased affinity for the drug. Another serious problem is that of resistance in certain gram-negative bacilli due to extended-spectrum beta-lactamase production ^[31].

Chapter 3: General Side Effects of IV Therapy

IV therapy can sometimes cause minor issues such as irritation or pain at the site of injection due to yeast over growth. More specifically, IV antibiotics may also be given in much higher doses due to the patient condition, severity and/or type of infection. For instance, pregnant women are given IV medication for group B strep bacteria because oral versions do not effectively kill the bacteria in the vagina to offer protection for the baby^[9].

Migration of skin organisms at the insertion site into the cutaneous catheter tract with colonization of the catheter tip is the most common route of infection for peripherally inserted, short-term catheters. Contamination of the catheter hub contributes substantially to intraluminal colonization of long-term catheters^[5].

When selecting vascular access devices and treatment regimens, it is important to consider the patient's lifestyle as well as clinical situation. For example, younger patients have different needs and considerations compared to older patients who are geriatrics. Some individuals have access to supportive caregivers while others are socially isolated. Some patients have the mental capacity and manual dexterity to be involved in their infusion therapy while others may not^[4,5]. These factors, as well as those unique to the patient's particular case, need to be taken into consideration when assessing for infusion therapy. Registered nurses undertaking the insertion of vascular access devices must undergo theoretical and practical training in the following^[5]:

- Anatomy and physiology of the circulatory system, in particular, the anatomy of the location in which the device is placed including veins, arteries and nerves and the underlying tissue structures
- Assessment of patients' vascular access needs, nature and duration of therapy and quality of life
- improving venous access, for example the use of pharmacological and non-pharmacological methods
- Selection of veins and problems associated with venous access due to thrombosed, inflamed or fragile veins, and the effects of ageing on veins, disease process, previous treatment, lymphoedema or presence of infection
- Selection of device and other equipment
- Infection control issues (hand-washing, skin preparation)
- Pharmacological issues (use of local anesthetics, management of anxious patients, management of hematoma, phlebitis, etc.) In the event of tenderness at the site, fever without an obvious source, symptoms of local or systemic infection, or the presence of exudates, the dressing should be removed and the site assessed.
- Documentation in the patient's nursing notes should reflect routine assessment and describe the condition of the insertion site.
- Patient education regarding dressing care and maintenance should be documented in the patient's notes ^[5].

Chapter 4: Mucosa Membrane

Buccal delivery relies on the properties of mucosa membranes found in the mouth. Mucosa Membranes are linings that are of endodermal origin. These linings are covered in epithelium and are responsible for absorption and some secretion. Body cavities that are exposed to the external environment and internal organs are lined with mucosa membrane^[7,8]. Several places in the body have continuous mucosa with skin – at the nostrils, the lips, the ears, the genital area, and the anus. The sticky thick fluid secreted by the mucous membranes and gland is termed mucus ^[8].

Different absorptive mucosa membranes, such as nasal, rectal, vaginal, ocular and oral cavity, are considered as potential sites for noninvasive systemic administration, local targeting / systemic drug delivery ^[19]. These drug delivery systems utilize property of bio-adhesion of certain water soluble polymers which become adhesive on hydration and therefore can be used for targeting particular sites. Buccal delivery is the administration of the drug via buccal mucosa (lining of the cheek) to the systemic circulation ^[8].

Types of Mucosa

1. Buccal mucosa
2. Esophageal mucosa
3. Gastric mucosa ^[8]
4. Intestinal mucosa
5. Nasal mucosa

6. Olfactory mucosa
7. Oral mucosa
8. Bronchial mucosa
9. Uterine mucosa^[7,8]

Anatomy and Physiology of Oral Mucosa

A thick dense & multilayered mucous membrane lines the oral cavity. This lining is highly vascularized. Drug penetrating into the membrane passes through a network of capillaries & arteries and reaches the systemic circulation [5].

There are mainly three functional zones of oral mucosa:

1. Masticatory mucosa : Covers gingival hard palate regions, keratinized epithelium
2. Mucous secreting region: Consist of soft palate, floor of mouth underside of tongue & buccal mucosa. This region shows non-keratinized mucosa.
3. Specialized mucosa : consist of lip border & dorsal surface of tongue with high selective keratinization^[8]

Components of Oral Mucosa

1. Epithelium
2. Lamina propria
3. Smooth muscle/Muscularis mucosa/ GI tract^[7]

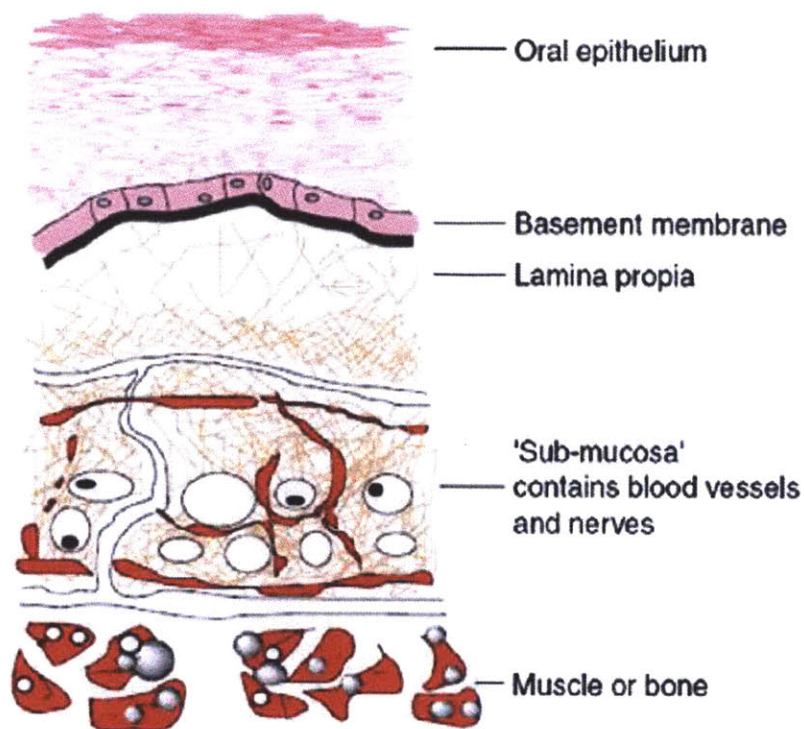


Figure 2: Schematic Diagram of Buccal Mucosa ^[4]

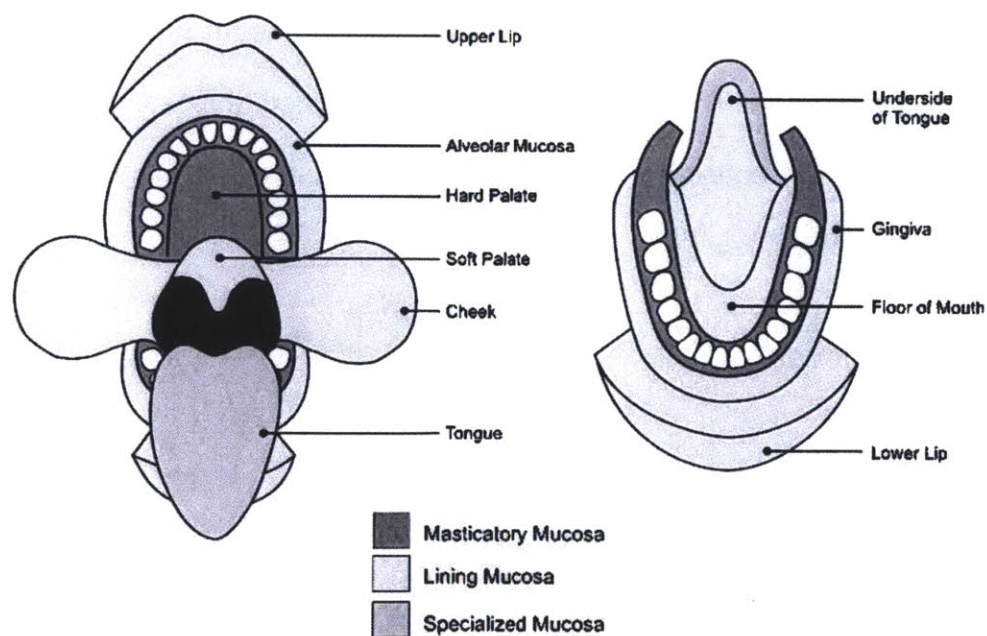


Figure 3: Schematic Diagram of the Mouth shows the anatomic location and extent of Masticatory, lining, and specialized mucosa in the oral cavity ^[38].

Region	Average epithelial thickness (um)
Skin (mammary region)	100 – 120
Hard palate	250
Buccal mucosa	500 – 600
Floor of mouth	100 – 200

Table 1: Different Epithelial and their thicknesses^[7]

Chapter 5: In-Depth Analysis of Buccal Drug Delivery

Concepts of Buccal Drug Delivery System

Mucoadhesive polymers are drug delivery vehicles. The common principle underlying this drug administration route is the adhesion of the dosage form to the mucous layer until the polymer dissolves or the mucin replaces itself. Benefits for this route of drug administration are: prolonged drug delivery, targeted therapy and often improved bioavailability ^[7].

Biological membrane, the membrane of internal tract such as GI Tract, buccal cavity, eye, nose, vagina, and rectum, are covered with a thick gel like structure known as *mucin*. All biological formulation interacts with mucin layer during process of attachment. It acts as a link between the adhesive and the membrane ^[7].

Mucous is a network of mucin glycoprotein that forms a continuous layer that intimately covers the internal tract of body. Total weight of mucous secreted by goblet cell only contains less than 5% of glycoprotein. There are about 160-200 oligosaccharides side chain in the glycosylated region of the glycoprotein.

Each oligosaccharides unit has 8-10 monosaccharides and terminal end of either sialic acid or L-fucose. Mucin has network of negative charge due to sialic acid, and sulfate residue. The bioadhesion mainly depends upon the nature of bioadhesive polymer. First stage involves an intimate contact between a bioadhesive & a membrane. Second stage involves penetration of the bioadhesive into tissue. At physiological pH the mucous network may carry negative charge because of presence of sialic acid & sulfate

residue and this high charge density due to negative charge contributes significantly to bioadhesion ^[8].

Advantages of Buccal Drug Delivery Systems

1. Termination of therapy is possible
2. Permits localization of drug to the oral cavity for extended period of time.
3. Ease of administration
4. Avoids first pass metabolism.
5. Reduction in dose can be achieved, thereby reducing dose dependent side effects
6. Allows for local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response, thus selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
7. Drugs that are unstable in the stomach's acidic environment or destroyed by the intestine's alkaline environment can be given by this route.
8. Drugs that show poor bioavailability by oral route can be administered by this route.
9. It follows passive diffusion and does not require any activation
10. The presence of saliva ensures large amount of water for dissolution of drug unlike in case of rectal and transdermal route ^[8].
11. Drugs with short half life can be administered by this method. (2-8 hrs) e.g.: nitroglycerine (2 hrs) isosorbide mononitrat^e (2-5^{hrs}).

12. From the formulation point of view, a thin mucin film exists on the surface of oral cavity.
13. Provides opportunity to retain delivery system in contact with mucosa for prolonged period of time with the help of mucoadhesive compounds.
14. The buccal membrane is sufficiently large to allow delivery system to be placed at different sites on the same membrane for different occasions, if the drug or other excipients cause reversible damage or irritate mucosa ^[8].

Disadvantages of Buccal Drug Delivery Systems

1. Over hydration may lead to formation of slippery surface & structural integrity of the formulation may get disrupted by the swelling & hydration of the bioadhesive polymer.
2. Eating and drinking may become restricted.
3. There is possibility that the patient may swallow the tablet ^[8].
4. The drug contained in swallowed saliva follows the peroral route thereby losing the advantages of the buccal route.
5. Only drug with small dosing requirements can be administered.
6. Drugs that irritate mucosa, have a bitter and/or unpleasant taste, or an obnoxious odor cannot be administered by this route ^[8].
7. Drugs that are unstable at buccal pH cannot be administered by this route.
8. Only those drugs which are absorbed by passive diffusion can be administered by this route ^[8].

Chapter 6: Buccal Delivery Drugs and Patches

Drug Characteristics for Buccal Drug

1. Molecular size – 75-600 daltons
2. Molecular weight between 200-500 daltons.
3. Drug should be lipophilic or hydrophilic in nature.
4. Stable at buccal pH.
5. Taste – bland
6. Drug should be odorless.
7. Drugs absorbed only by passive diffusion should be used ^[8].

Formulations used for buccal delivery



Photo of different formulations [17]

Oral bioadhesive formulation

1. Corlan – hydrocortisone succinate
2. Bonjela – hypromellose
3. Taktarin – miconazole^[8]

4. Corsodyl – chlorohexidine^[8]

Buccal mucosa drug formulation

1. Buccaten – nausea , vomiting, vertigo^[8]
2. Suscard - angina
3. Oxytocin Buccal Tablets (too large to be administered sublingually)^[18]

Sublingual formulation

1. GTN (Glycerin Trinitrate)^[8]

Permeability Enhancer formulation

Permeability enhancers are substances added to pharmaceutical formulation in order to increase the membrane permeation rate or absorption rate of co-administered drug. They can enhance the drug's bioavailability by 5% to 40%. The limiting factor in using strong permeation enhancers is the potential for membrane damage. For example the permeability of fluorescein isothiocyanate (FITC) has increased 100-200 fold compared to FITC alone by simply using di- and tri-hydroxyl bile salts as a permeation enhancer^[8].

Design of Buccal Dosage Form

Buccal Patches

The use of polymeric patches for buccal delivery has not yet been widely investigated, although they have been extensively employed in the modification of the drug release and their protection by way of coating and matrix formation in various solids like tablets, pellets, granules and powders. An ideal buccal patch should be flexible, elastic and soft yet adequately strong to withstand breakage due to stress from mouth activities.

Moreover, it must also exhibit good mucoadhesive strength so that it can be retained in the mouth for a desired duration. As such, the mechanical, mucoadhesive, and swelling properties of buccal patches are critical and essential to be evaluated ^[7, 8].

As mentioned before, the buccal route has high acceptance due to avoidance of first pass metabolism and possibility of being accessible for controlled drug release. Buccal patches are preferred over adhesive tablets in terms of flexibility and patients comforts.

A suitable buccal drug delivery system should be flexible and possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a predictable manner to elicit the required therapeutic response ^[31].

Buccal patches are laminates that could contain an impermeable backing layer, a drug-containing reservoir layer, and a bioadhesive surface for mucosal attachment, which are similar to those used for transdermal drug delivery. Backing layer control the direction of drug release, prevent drug loss, minimize deformation and disintegration ^[31].

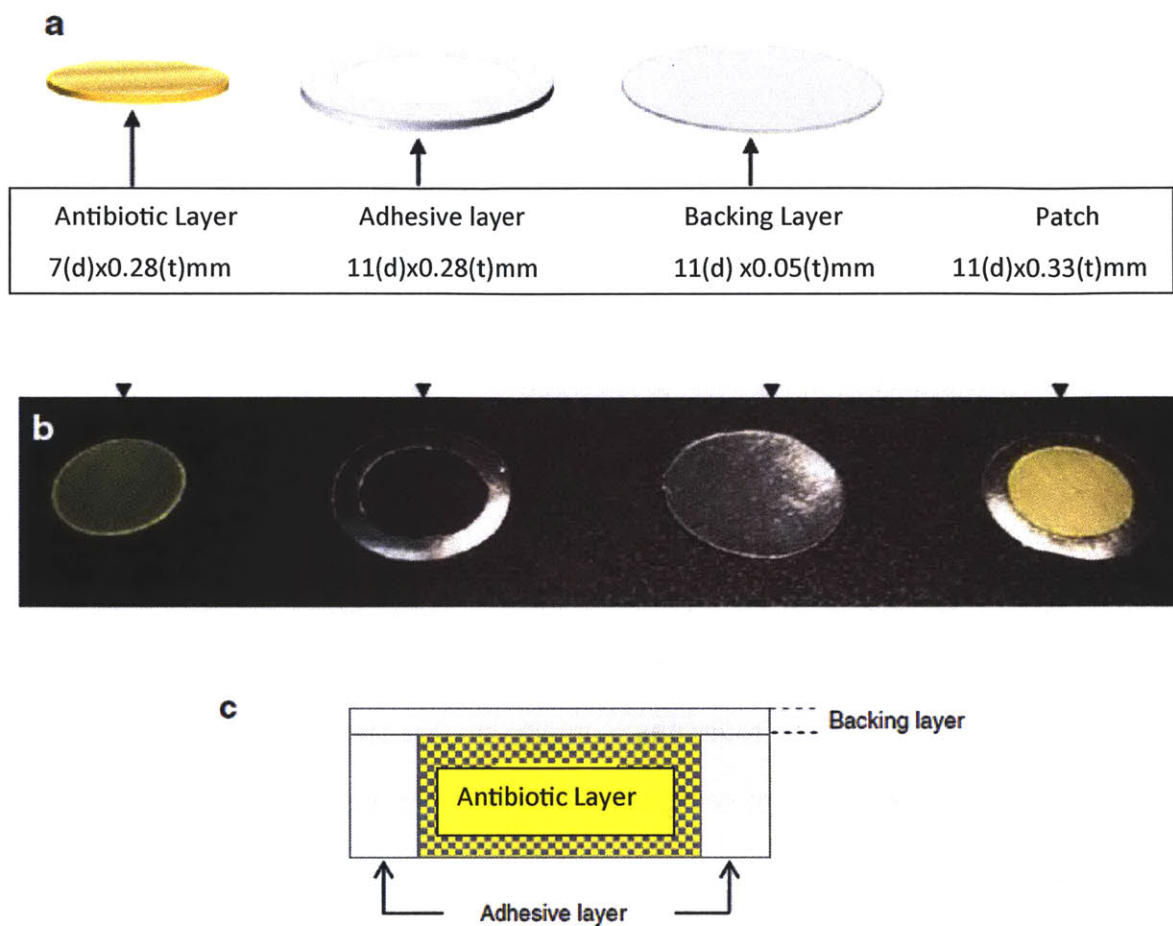


Figure 4: Schematic diagram: (a), photographic image (b), and schematic cross-sectional diagram (c) of a Mucoadhesive patch comprising drug ^[18]

Matrix Type

The Buccal patch designed in a matrix configuration contains drug, adhesive, and additives mixed together. Bi-directional patches release drug in both the mucosa and the mouth. The structure of the matrix type design is basically a mixture of the drug with the mucoadhesive matrix.

Reservoir Type

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. Impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss.

Other buccal delivery methods

Buccal Films

This is a recent method of buccal drug delivery which is more user friendly than the buccal adhesive tablet. It is beneficial for oral diseases because of its strength, softness, adhesiveness and flexibility.

Buccal Gels

These semisolid dosage forms are easy to disperse throughout the oral mucosa but are not as accurate as tablets, patches, or films. Poor retention of the gels at the site of application has been managed by using bioadhesive formulations.

Challenges of Buccal Delivery

Oral transmucosal and the environment of the oral cavity present some significant challenges for systemic drug delivery. In order for the drug to enter the systemic circulation it needs to be released from the formulation to the delivery site (e.g. buccal or sublingual area) and pass through the mucosal layers ^[8]

Drug Encapsulated Nano particles

The following figure shows the three stages of drug delivery via nano encapsulation

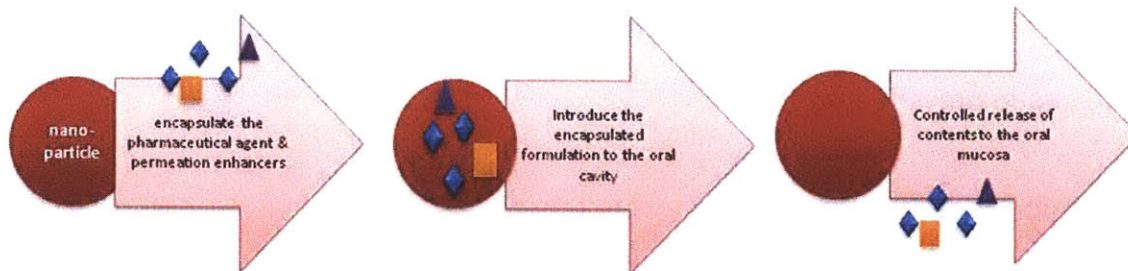


Figure 5: Nano Encapsulation & Release

Drug permeation is impacted by the certain physiological aspects of the oral cavity ^[8] such as:

1. Oral cavity's mucosa health and age
2. Fluid volume
3. Enzyme activity

For extended release drug delivery the following are major factors ^[8]:

1. mucoadhesivity
2. Structure of the mucosa surface area
3. Turnover of the mucosa cells more

Absorptive site	Estimated surface area	Percent total surface area	Local pH	Mean fluid volume (ml)	Relative enzyme activity	Relative drug absorption capacity
Oral cavity	100 cm ² (0.01 m ²)	0.01	5.8-7.6	0.9	Moderate	Moderate
Stomach	0.1-0.2 m ²	0.20	1.0-3.0	118	High	Moderate
Small intestine	100 m ²	98.76	5.0-7.0	212	High	High
Large intestine	0.5-1.0 m ²	0.99	6.0-7.4	187	Moderate	Low
Rectum	200-400 cm ² (0.04 m ²)	0.04	7.0-7.4	-	Low	Low

Table 2: Comparison of different mucosa^[7]

Table 2 shows the comparison between buccal mucosa with the mucosa of the GI tract based on their physiological characteristics^[7].

Role of saliva and mucus in the buccal delivery

As mentioned earlier, saliva produced in the oral cavity plays a key role in the drug permeation. Therefore, it is important to understand the function and variability of saliva and its producing glands. The main functions of saliva are to lubricate the oral cavity, facilitate swallowing, and prevent demineralization of the teeth. Saliva allows carbohydrate digestion and regulates oral microbial flora by maintaining the oral pH and enzyme activity. Saliva's pH significantly influences the drug permeability and is considered a weak buffer with a pH around 5.5–7.0^[2, 7].

Salivary glands produce mucus, which surrounds the oral epithelia cells. The mucus complexes are made up of proteins and carbohydrates; with thickness ranging from 40

to 300 µm. In the oral mucosa, mucus is secreted as part of saliva by the major and minor salivary glands and is mostly made up of water. However, it has key macromolecular glycoprotein components known as mucins (1–5%). Mucins contain large amounts of carbohydrate with molecular mass ranging from 0.5 to over 20 MDa and are made up of basic units (≈400–500 kDa) linked together into linear arrays forming an extended three-dimensional network ^[7]. Mucins act as a lubricant allowing. Mucins act as a lubricant allowing cells to move relative to one another, and may also contribute to cell–cell adhesion. The mucus network is negatively charged due to the sialic acid and sulfate residues and forms a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. It is believed that this gel layer extends the dosage form retention time at the delivery site thereby allowing the drug to stay stationary longer ^[2, 7].

The following are some of the relative facts about saliva:

Major salivary glands in the oral cavity are ^[8]:

1. Parotid (watery secretion)
2. Submaxillary (watery secretion)
3. Sublingual (viscous saliva with limited enzymatic activity)

Minor salivary glands ^[8]

1. Buccal glands (right below the mucosa)

Saliva volume:

1. Daily secretion volume: 0.5 to 2.0 liter

2. Constant volume present in the mouth: 1.1 milliliter
3. Lower volume and less viscous compared to GI fluid^[8]

The flow rate of saliva which determines the oral cavity's pH and salivary compositions are dependent on ^[8]:

1. Time of day,
2. Type of stimulus
3. Degree of stimulation.

High flow rates of saliva, causes increase of sodium and bicarbonate concentrations which in turn increases the pH of the oral cavity. The water rich environment in the oral cavity can be favorable for the release of the drug from delivery systems especially those that are based on hydrophilic polymers, but too much flow can lead to premature swallowing of the drug before effective absorption occurs through the oral mucosa called "saliva wash out"^[2,3,7].

Oral Mucosa Permeation

Drug permeability through the oral (e.g. buccal/sublingual) mucosa is another major physiological barrier for oral transmucosal drug delivery. The thickness of oral mucosal and the composition of the epithelium vary depending on the site ^[7, 37].

The characteristics of the different regions of interest in the oral cavity are shown in Table 3.

Tissue	Structure	Thickness (μm)	Turnover time (days)	Surface area (cm ² ±SD)	Permeability	Residence time	Blood flow
Buccal	NK	500–600	5–7	50.2±2.9	Intermediate	Intermediate	20.3
Sublingual	NK	100–200	20	26.5±4.2	Very good	Poor	12.2
Gingival	K	200	–	–	Poor	Intermediate	19.5
Palatal	K	250	24	20.1±1.9	Poor	Very good	7.0

Table 3: Different Tissues in the oral cavity^[7]

Note that mechanical stress on different areas of mucosa impacts the keratinization characteristic of the area. For example the mucosa of the soft palate, sublingual and buccal regions are not keratinized which makes them more suitable for drug delivery. The neutral lipids in keratinized epithelia are associated with the barrier function which makes them relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia do not contain acylceramides and only have small amounts of ceramides which makes them more permeable to water. They have neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. ^[7]

There intercellular materials derived from the so-called membrane coating granules (MCGs) contribute to the relative impermeability of the oral mucosa. MCGs organelles (100–300 nm in diameter) are found in keratinized and non-keratinized epithelia. Cultured oral epithelium without MCGs is more permeable for delivery of compounds than normal epithelium. Also permeation studies with the use of tracers show that tracer molecules cannot penetrate below the top 1-3 layers of normal epithelium where MCGs are observed. When the same tracer molecules were introduced sub-epithelially, they penetrated through the intercellular spaces. This same pattern is observed in both

keratinized and non-keratinized epithelia, which indicates that MCGs are more significant to permeation compared to the keratinization of the epithelia. Another factor of the buccal epithelium that can affect the mucoadhesion of drug delivery systems is the turnover time^[7]. As mentioned above mucus is a key contributor to the mucoadhesion but so is the turnover time. The turnover time for the buccal epithelium is estimated to be 3–8 days compared to about 30 days for the skin^[7]. The turn over time also contributes to the resilience of the mucosa's epithelium layer since it can recover quickly from damages caused by minor drug irritations. There are about 40 – 50 layers of cell in the buccal mucosa, resulting in about 500 – 600 μm thick [2, 37]. The following figures illustrate the drug absorption mechanisms and approaches for the delivery of drugs through the oral mucosa.

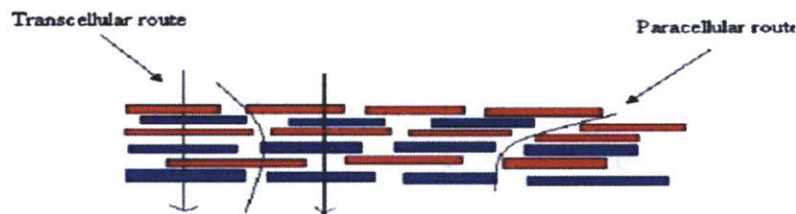


Figure 6. Cellular Drug Absorption Mechanism^[7]

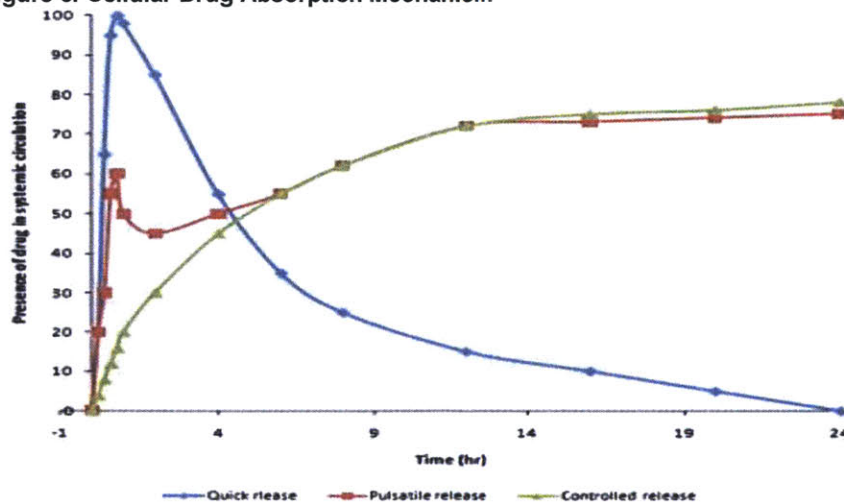


Figure 7, Drug Delivery Approaches ^[7]

Buccal Delivery Verses Oral Delivery for Replacing Injection

The oral delivery remains the preferred route for drug administration due to its low cost, ease of administration and high level of patient compliance. However due to the significant restrictions of drug delivery within the gastrointestinal (GI) tract, other absorptive mucosae are being considered as potential sites for drug administration including the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. These transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery such as the possible bypass of the first pass effect and avoidance of presystemic elimination within the GI tract. Amongst these, drug delivery to the oral cavity has attracted particular attention due to its potential for high patient compliance and unique physiological features ^[7, 8]. Within the oral mucosal cavity, the delivery of drugs can be classified as follow:

1. Local delivery
2. Systemic delivery either via the buccal or sublingual mucosa ^[8].

Despite the challenges of systemic delivery via oral mucosa, this area has unique structural and physiological properties. The properties offer several opportunities for effective delivery of certain class of drugs to the blood stream ^[8]. As the mucosa is highly vascularized and any drug diffusing across the oral mucosa membranes has direct access to the systemic circulation via capillaries and venous drainage and will bypass hepatic metabolism. As shown in table 3, the rate of blood flow through the oral

mucosa is substantial, and is generally not considered to be the rate limiting factor in the absorption of drugs by this route^[8].

The following list is the summary of some of the challenges with oral drug delivery:

1. For oral delivery through the GI tract, the drug undergoes a rather hostile environment before absorption
2. GI track includes drastic changes in pH (from pH 1–2 in the stomach to 7–7.4 in the distal intestine)
3. GI transit is unpredictable, caused by the presence of numerous digestive enzymes and intestinal flora^[8]

Unlike this harsh environment of the GI tract, the oral cavity offers relatively consistent and friendly environment for drug delivery which include some of the following conditions:

1. Continuous secretion of saliva.
2. Saliva is a relatively mobile fluid with less mucin than the GI tract
3. Limited enzymatic activity
4. Almost no protease in the oral cavity^[8].

The degradation of protein and peptide due to GI track's enzymes is a major concern for oral drug delivery. In comparison, the buccal and sublingual regions have less enzymes and lower enzyme activity. It is believed that the buccal mucosa is exposed to mainly some aminopeptidases, carboxypeptidases which are relatively mild compare to the GI track enzymes.

Despite the tremendous advances in the oral mucosa drug delivery, the oral-GI route remains the preferred route for drug administration due to its low cost, ease of administration and high level of patient compliance. However, this review examines the physiological considerations of the oral cavity in light of systemic drug delivery and provides an insight into the advances in oral transmucosal delivery systems.

Name of Drug	Transport Mechanism	Pathway	Tissue
5-Aza-2'-deoxycytidine	Passive	Not Defined	Buccal mucosa
2', 3'- dideoxycytidine	Passive	Not Defined	Buccal mucosa
Flecainide	Passive	Paracellular	Buccal mucosa
Sotalol	Passive	Paracellular	Buccal mucosa
Nicotine	Passive	Paracellular, Transcellular	TR146 Cell culture and buccal mucosa
Lamotrigine	Passive	Transcellular	Buccal mucosa
Galantamine	Passive	Not Defined	Human oral epithelium and buccal mucosa
Naltrexone	Passive	Not Defined	Buccal mucosa
Buspirone	Passive	Transcellular	Buccal mucosa
Ondansatron HCl	Passive		Buccal mucosa
Monocarboxylic acids	Carrier Mediated	Carrier Mediated	Buccal mucosa
Glucose	Carrier Medicated	Carrier Mediated	Primary cultured epithelial cells
			Buccal, oral mucosal cells and dorsum of tongue

Table 4: Examples of Drugs Transported via Different Mechanisms through Buccal Mucosa^[7]

To maintain antimicrobial activity, antibiotics with short half-life should be frequently administered. If not followed concentration under MIC (minimum inhibitory concentration) occurs frequently in the course of anti-infective treatment, which induces antibiotic resistance. By maintaining a constant plasma drug concentration over MIC for a prolonged period, extended-release dosage forms maximize the therapeutic effect of antibiotics while minimizing antibiotic resistance. Another undoubted advantage of extended-release formulation is improved patient compliance^[32]. The buccal delivery can support extended antibiotic delivery relative to oral delivery to reduce the chance antibiotic resistance, however since the bioavailability is not as good as intravenous

delivery, there is always a chance that the amount of antibiotic delivered via the buccal tissue is not adequate relative to IV delivery. Ultimately to better measure and understand the challenges and benefits of the buccal antibiotic delivery, PK/PD studies need to be performed (see Appendix G for details) ^[36].

As mentioned above the bioavailability of the drug via the buccal tissue is not very high, even with the addition of permeation enhancers and Mucoadhesive compounds to the drug composition, the bioavailability of buccal delivery could be only about 20% of the intravenous (IV) delivery. To cause the same effect as IV delivery, there needs to be 80% more antibiotic in the buccal area which offers problems such as toxicity and cost.

Some of the broad spectrum IV antibiotics on the market require large doses and these drugs due to the bioavailability limitations of mucosa membrane will not be good candidates for buccal delivery. Many of these antibiotics are also very costly about \$400 per dose which would also be a barrier to entry for buccal delivery due to the limited bioavailability ^[2, 7]. The other limiting factor for some antibiotics is that the patch or oral mucosa delivery devices can contain small amounts of drugs so we assumed maximum 11 mg of drugs. The matrix limitation and nano encapsulation of the drug contribute to this limitation.

If the antibiotic's side effects include tissue irritation then buccal delivery might not be good delivery method for that antibiotic.

Chapter 7: Antibiotic Marketing and Business Requirements

This thesis's Marketing Consideration

This research takes in to consideration the following key marketing and business elements for selecting the best antibiotics for buccal delivery:

- Market size for the injectable antibiotics
- Patient Eligibility
- Cost
- Availability
- Location
- Regulatory Landscape :
 - guidelines
- Important stakeholders
 - Existing products
 - Locality of trials
 - US based
 - Developing countries
 - Emerging policies
 - Relevant precedents
- End customer:
 - Hospitals
 - Insurance companies

- Company Investors
- Care givers
- Patients

Market Need

Microbial natural products are the origin of most of the antibiotics on the market today. However, research in antibiotics and natural products has declined significantly during the last decade as a consequence of diverse factors and has caused an alarming scarcity of new antibiotic classes in the pipelines of the pharmaceutical industry ^[11].

Looking into the future demands for antibiotics; now is a great time to investigate and start businesses around antibiotics to meet the upcoming demands ^[11].

Moreover, several popular antibiotics are coming off patent and there is an interest in the pharmaceutical market to extend their existing patents' life through alternative drug delivery techniques. Based on our research, offering these companies alternative and reliable buccal delivery of their antibiotics would be of great value.

Buccal Delivery – An Effective Response to Clinical Needs

Healthcare-associated infections (HAI) result in excess length of stay, mortality and healthcare costs. In 2002, an estimated 1.7 million healthcare-associated infections occurred in the United States, resulting in 99,000 deaths. In March 2009, the CDC released a report estimating direct medical costs of healthcare-associated infections that ranged from \$28-45 billion annually ^[6].

- In the US alone, bloodstream infections are the 8th cause of death.
- Prevention from infection is a major focus of healthcare providers, because risk of death from bacteremia or fungemia is very high.
- According to CDC, 35 million patients are annually admitted to 7000 US based acute-care units.
- Since infection is the most common serious complication of intravascular catheters causing high morbidity and mortality the benefits derived from these devices are seriously being questioned.
- Most catheter-related infections are caused by staphylococci, originating from the skin of the patient and migrating along the external surface of the catheter^[6].
- Prolonged duration of catheter placement, frequent manipulation of the catheter and use of thrombogenic catheter material increase the risk of infections^[6].

Critical Care Antibiotic Market:

According to “Frost and Sullivan”, critical care antibiotics are used in hospital and intensive care settings to treat patients with ^[10]:

- Nosocomial or hospital-acquired infections
- Serious community-acquired infections requiring

Critical care antibiotics cost ~\$62.50 per day, 5 million prescriptions annually. The bullets below reflect the current reality that the market is dominated by intravenous/intramuscular injectable antibiotics^[10].

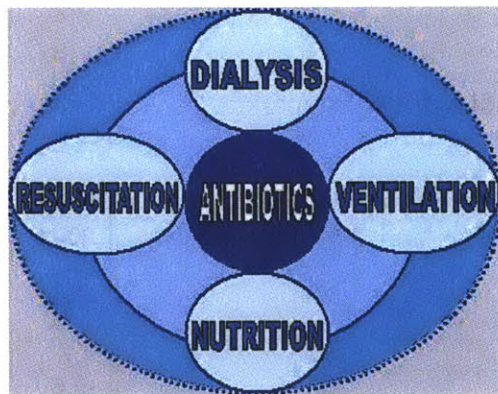
- Market size (2002) of \$3.14 billion growing at 4%
- Market potential (2009) of \$3.76 billion at CAGR 3% ^[10]

“Frost and Sullivan” describes the different aspects of antibiotics as follow ^[10]:

- Critical Care Antibiotics are an integral part of life-sustaining or life-saving technologies.
- Antibiotics: IM / IV injections to treat primary / secondary / nosocomial infections

Common uses (see figure 8):

- **Ventilation:** mechanical or machine-assisted ventilation
- **Resuscitation:** cardiopulmonary resuscitation for patient in cardiac arrest



- **Dialysis:** may be renal dialysis, hemodialysis or peritoneal dialysis.
- **Nutrition:** includes nutritional substances and hydration (tube and IV feeding)

Figure 8: Antibiotic Uses in the Hospital ^[10]

Market Segmentation

Critical Care (Hospital) Antibiotics

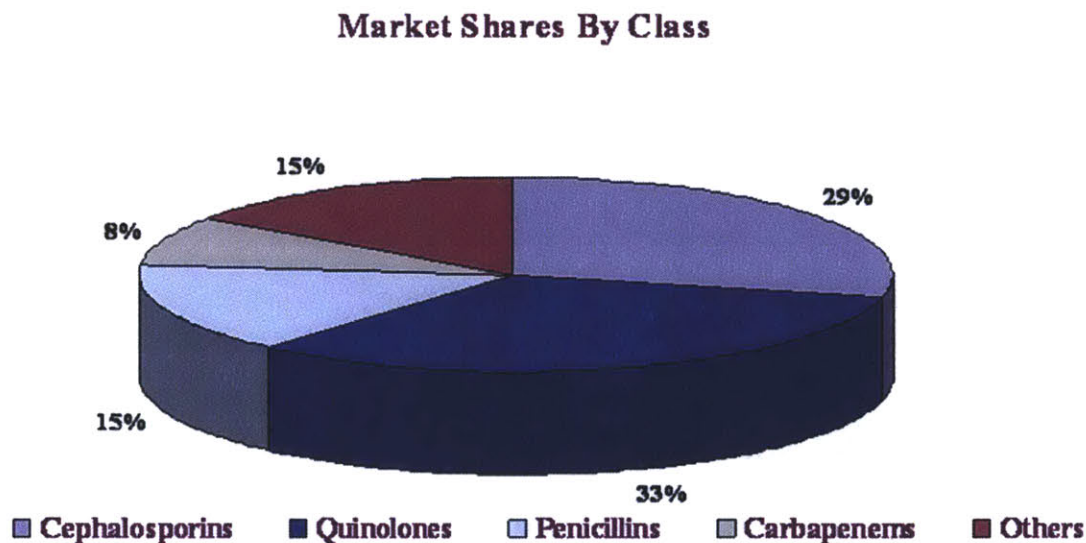
CEPHALOSPORINS Ancef (Cefazolin) Cefotan (Cefotetan) Claforan (Cefotaxime) Fortaz (Ceftazidime) Kefzol (Cefazolin) Maxipime (Cefepime) Mefoxin (Cefoxitin) Rocephin (Ceftriaxon)	PENICILLINS Timentin (Ticarcillin-Clavulanate) Unasyn (Ampicillin-Sulbactam) Zosyn (Piperacillin-Tazobactam)	OTHERS NEWER Streptogramins: Synercid (Quinopristin-Dalfopristin) Oxazolidones: Zyvox (Linezolid) OLDER Lincosamides: Cleocin (Clindamycin) Glycopeptides: Vancocin (Vancomycin) Macrolides: Zithromax (Azithromycin) Aminoglycosides: Nebcin (Tobramycin)
QUINOLONES Avelox (Moxifloxacin) Cipro (Ciprofloxacin) Factive (Gemifloxacin) Tequin (Gatifloxacin)	CARBAPENEMS Primaxin (Imipenem-Cilastatin) Merrem (Meropenem) Invanz (Ertapenem)	
	<i>Only Branded Injectables Included</i>	

Table 5: Market Overview^[10]

Quinolones, carbapenems and new antibiotics drive the market^[10]:

Antibiotic Class	Market Size 2002 \$ Million	Growth 2002 %	Potential 2009 \$ Million	CAGR % 2003- 2009
Cephalosporins	908	1	870	-0.6
Quinolones	1019	6.8	1405	4.7
Penicillins	474	2	457	-0.5
Carbapenems	263	11	381	5.5
Others	479	0.6	648	4.4
Total	3143	4	3760	3

Table 6: Common antibiotic classes^[10]



Others: Streptogramins, Oxazolidones, Macrolides, Aminoglycosides, Lincosamides, Tetracyclines, Glycopeptides

Figure 9. Major classes of Antibiotics' Market share ^[10]



Figure 10: Technology and market trends ^[10]

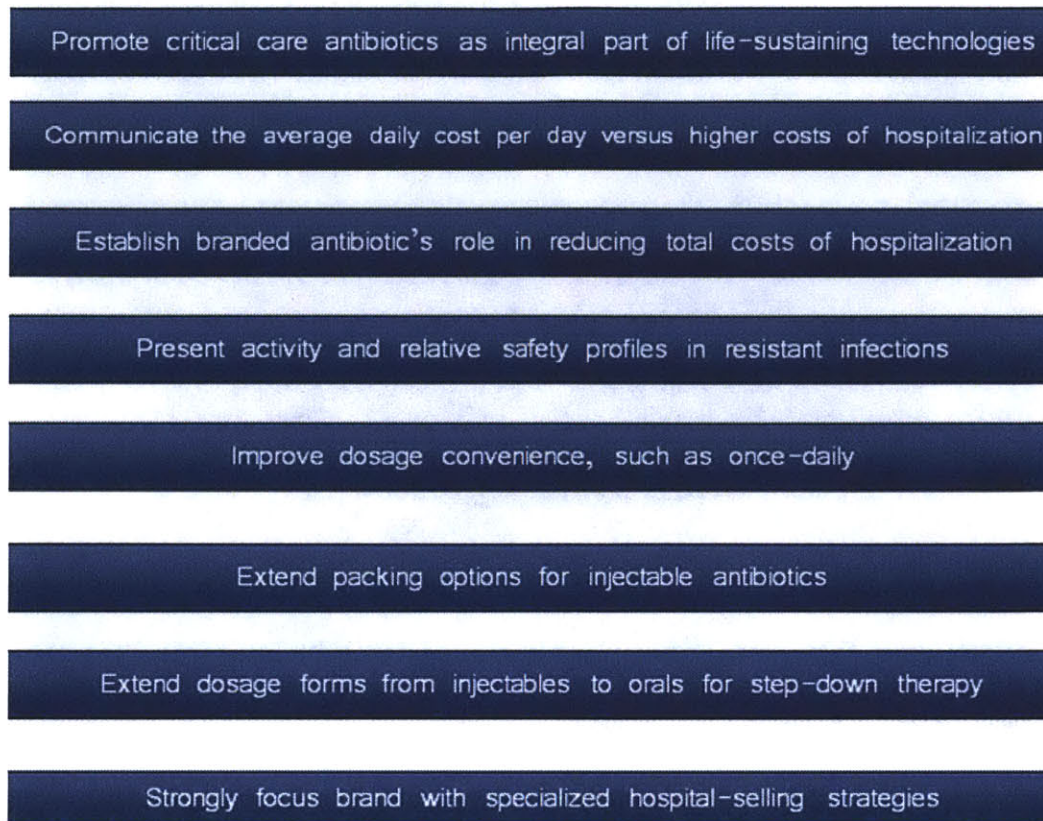


Figure 11: Growth strategies ^[10]

Chapter 8: Requirements for this Research

Scientific and Clinical Considerations

1. Drug's Molecular Size
2. Dosage
3. Side effects
4. Bio-activity
5. Bio-availability
6. Half Life of the drug
7. Frequency of the Drug prescription
8. Number of doses per day
9. Antibiotic Resistance
10. Physician's input

Business Considerations

1. Market Size
2. Dosage Price
3. Patent status (how many years left on the patent life)
4. US market
5. Global Market

Buccal Delivery Considerations

1. Limitations of buccal tissue
2. Toxicity

3. Preexisting conditions
4. pH of the mouth
5. Age ^[2,7,8,10,11]

Best Candidate Drugs for Use in Nano Particle Buccal Patch.

- Assumed 11 mg entering bloodstream per buccal patch
- Platform-compatibility
 - Molecular size
 - Low dosage
 - Non-oral administration
 - Market Size
- Patent status
- Side Effects

This investigation started with 150 antibiotics and based on the criteria's mentioned above reduced the choices down to 4 best candidates

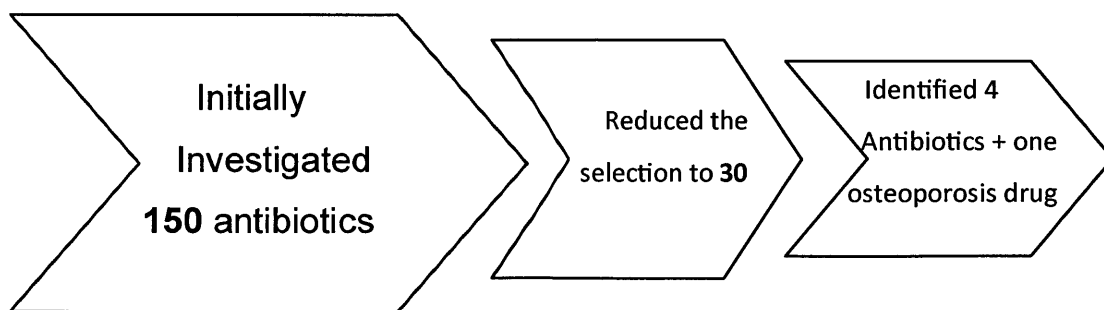


Figure 12: Narrowing down the drug candidates

	Name	Daily Dose	Market	Under Patent
1	Terparatide	1	\$219M (US 2010)	yes
2	Cancidas	5	\$611M (US 2010)	yes
3	Tygacil	5	\$179M (US 2009)	yes
4	Enfuvirtide	10	\$134M (US 2006)	yes
5	Daptomycin	29	\$415M (US 2008)	yes
6	Gentamycin	9	\$140M (US 1990)	no
7	Targocid	17	\$358M (US 2002)	no
8	Rocephin	21	\$740M (US 2005)	no
9	Colistimethate	21	\$15.4M (US 2007)	no
10	Ceptaz	21	\$42M (US 2008)	no
11	Cidofovir	32	\$2.6M (US 2002)	no
12	Imipenem	21	\$25M (US 2011 Q1)	no

Table 7, Examples antibiotic that made our second round of filtering

Chapter 9: Final Drug Candidates

Caspofungin (Cancidas)

Caspofungin is an antifungal drug marketed by Merck & Co under the brand name Cancidas. It is part of a new class of antibiotics called the echinocandins. It works effectively on *Aspergillus* and *Candida* fungi by inhibiting the enzyme $\beta(1,3)$ -D-Glucan synthase and thereby destroying the fungal cell wall. Caspofungin is administered intravenously^[24].

Dosage	Market	Main use:	Side Effects
5/dose	US: \$611M (2010)	Infections with <i>Aspergillus</i>	No skin effects listed in common side effects
Taken daily for 2 weeks	Global: \$617M (2009)	Infections with <i>Candida</i>	Low incidence of side effects including headache, nausea, diarrhea, fever, phlebitis
Blood level monitoring when used in conjunction with certain drugs	\$411.84 / dose		
IV infusion over 1 hour	Patent Expires in 2015		Other Notes:
Mol. mass 1093.31 g/mol	Formula C ₅₂ H ₈₈ N ₁₀ O ₁₅		
Pros	Cons	Recommendation	
High demand Large market share Basal administration 2 nd lowest daily dosage	Slowed CAGR: sales have slumping with introduction of new echinocandins.	Very promising drug with the lowest dosage of all the antibiotics. Currently there is a large market size, although may want to look at more recent trends.	

Table 8, summary of Cancidas investigation^[24]

Caspofungin acetate for injection was originally approved in 2001. Its approved indications include the fungal infections in febrile, neutropenic adult patients and the treatment of invasive aspergillosis in adult patients whose fungal infection does not respond to other antifungal drugs (i.e., conventional or lipid formulations of amphotericin B and/or itraconazole). Additionally, the FDA approval includes indication for the treatment of candidemia and some specific *Candida* infections (intra-abdominal abscesses, peritonitis, pleural cavity infections and oesophagitis) and the EMEA approval includes indication for the treatment of general invasive candidiasis in adult patients.

Tigecycline (Tygacil)

A glycylcycline antibiotic, tigecycline marketed by Wyeth under the brand name Tygacil was given a U.S. FDA fast-track approval on June 17, 2005. It was developed in response to the growing prevalence of antibiotic resistance in bacteria such as *Staphylococcus aureus* and *Acinetobacter baumannii*. The New Delhi metallo- β -Lactamase multidrug-resistant Enterobacteriaceae has also shown susceptibility to tigecycline ^[22].

Dosage	Market	Main use:	Side Effects
10 for initial dose then 5/dose 2x a day	179M(US 2009)	Complicated Skin/Skin Structure Infections	No skin effects listed in common side effects
Taken twice daily for 2-4 weeks	\$90.46 / dose	Complicated Intra-abdominal Infections	Common side effects: diarrhea, nausea and vomiting.
Blood level monitoring IV			Other side effects include pain at the injection site, swelling and irritation; increased or decreased heart rate and infections.
Infusion for 30-60 minutes.	Patent expires April 2016	Community-Acquired Bacterial Pneumonia	Other Notes: Not recommended for children and pregnant women.
Mol. mass 585.65 g/mol	Formula C ₂₉ H ₃₉ N ₅ O ₈		
Pros	Cons	Recommendation: Distant 2nd	
Patented until 2016 Basal administration Lower dosage than most	Relatively small market, even though lower than most, still lots of patches to be used	At 10 patches daily, this could decrease patient's compliance. If dosage per patch could be increased it would be a good candidate, albeit in a relatively small market. Given the 2016 expiration date, this could be possible.	

Table 9, summary of Tigecycline investigation ^[21, 22].

Tigecycline is bacteriostatic and is a protein synthesis inhibitor. It does this by binding to the 30S ribosomal subunit of bacteria and thereby blocking entry of Aminoacyl-tRNA into the A site of the ribosome during prokaryotic translation. Tigecycline is administered intravenously and fights against some of gram-positive and gram-negative bacteria pathogens, which most are resistant to existing antibiotics. In phase 3 clinical trials it shows effectiveness similar or better than intravenous vancomycin and aztreonam. It was to treat complicated skin and skin structure infections (cSSSI), and to intravenous imipenem and cilastatin to treat complicated intra-abdominal infections (cIAI) ^[21,22].

Tigecycline is active against many Gram-positive bacteria, Gram-negative bacteria and anaerobes – including activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae* (with MIC values reported at 2mcg/mL) and multi-drug resistant strains of *Acinetobacter baumannii*. It has no activity against *Pseudomonas* spp. or *Proteus* spp. The drug is licenced for the treatment of skin and soft tissue infections as well as intra-abdominal infections ^[21, 22].

Tigecycline is slowly administered over 30 to 60 minutes by intravenous infusion. A single dose of 100 mg is given first, followed by 50 mg every twelve hours after that. Patients with impaired liver function need to be given a lower dose. No adjustment is needed for patients with impaired kidney function. It is not licensed for use in children and there is no oral form available ^[22].

Enfuvirtide (Fuzeon)

Enfuvirtide is an HIV fusion inhibitor, the first of a novel class of antiretroviral drugs used in combination therapy for the treatment of HIV-1 infection. Roche is currently markets it under the trade name Fuzeon. The average annual cost of treatment with this drug in the US is \$25,000. Due to its cost and inconvenient dosing regimen it is used as a "salvage" therapy in patients with multi-drug resistant HIV [25, 26, 27].

Dosage	Market	Main use:	Side Effects
20 daily (10/dose)	US + Canada: \$134 million (2006) Global: \$249 million (2006)	HIV-1	Injection site reactions are common, recommended to use different sites for every injection
Taken as long as patient benefits	\$35 / dose (\$25000/year)		Peripheral neuropathy, insomnia, depression, cough, dyspnoea, anorexia, arthralgia, infections , and eosinophilia
No blood-level tests	Patent Expires June 2013		
Bolus subcutaneous injection			Other Notes: Its cost and inconvenient dosing regimen are factors limiting its use to a reserve medication.
Mol. mass 4492.1 g/mol	Formula C202H298N50O64		
Pros	Cons	Recommendation	
Potentially taken continuously for life Patented until 2013	Common to have skin reactions 20 patches/day Bolus injection	Not a useful candidate at this time. It is thought that the market is currently limited due to the poor delivery system, which could make it a good match for Privo. However, the drug causes skin reactions which could be problematic for trans-mucosal delivery and the 20 sticks of gum daily exceeds Privo's stated maximum. The patent expires in 2 years, leaving little time to solve these issues.	

Table 10, summary of Enfuvirtide investigation [25, 26, 27]

Daptomycin (Cubicin)

Daptomycin is a new peptide antibiotic used for Gram-positive infections and is naturally found in the soil. Its mainly used for infections caused by multi-resistant bacteria and is marketed in the United States under the trade name Cubicin (Cubist Pharmaceuticals)

[28, 29, 30]

Dosage	Market	Main use:	Side Effects
29/dose	US: \$153.7m (2011 Q1)	Complicated skin	Skin reactions have been reported including Stevens-Johnson syndrome
Taken daily for 7-14 days	Global: \$162m (2011 Q1)	Bloodstream infections caused by gram-positive bacteria <i>Staphylococcus aureus</i> .	Anaphylaxis, gastrointestinal disorders, musculoskeletal disorders, respiratory disorders
IV infusion for 30mins	\$129 / dose		
.	Patent Expires in 2017		Other Notes: Its cost and inconvenient dosing regimen are factors limiting its use to a reserve medication.
Mol mass 1619.7 g/mol	Formula C ₇₂ H ₁₀₁ N ₁₇ O ₂₆		
Pros	Cons	Recommendation	
No reported drug resistance Large market Steady growth in sales over the past 5 years	Dosage too high for 11 mg/patch Serious skin side effects	Best of the Patented Higher-Dose Drugs Daptomycin would be a good candidate due to its large market and low resistance if the issues of the larger dosage and skin side effects can be resolved.	

Table 11, summary of Daptomycin investigation [28,29,30]

Daptomycin has been currently approved by the FDA for skin and Gram-positive skin structure infections, such as *Staphylococcus aureus* bacteraemia and right-sided *S. aureus* endocarditis. Unfortunately it cannot be used for the treatment of pneumonia since it binds tightly to pulmonary surfactant ^[28].

The effectiveness of Daptomycin is similar to standard therapies (nafcillin, oxacillin, flucloxacillin or vancomycin) in the treatment of bacteraemia and right-sided endocarditis caused by *Staphylococcus aureus*. It was used in a study in Detroit, Michigan on 53 patients suspected of having MRSA skin or soft tissue infection and the results were compared to those of vancomycin. The result suggested that Daptomycin is more effective due to faster recovery from skin and soft tissue infections (4 days versus 7 days). Although the vancomycin control results were from several years ago where the general patient treatment was not as advance as now and the dose was lower than (5mg/dl, compared to the 10mg/dl or 15mg/dl currently recommended).

Teriparatide (Forteo)

Even though Teriparatide is not an antibiotic, we noticed that it would be a great candidate for buccal delivery. This drug is a parathyroid hormone in a recombinant form, used in the treatment of some osteoporosis cases. It is manufactured and marketed by Eli Lilly and Company. This drug is also available in generic form and is our first choice for a buccal delivery drug ^[23].

Dosage	Market	Main use:	Side Effects
1 patch daily	US \$518.3M (2009) Global \$816.7M (2009)	Osteoporosis treatment	No skin effects listed in common side effects Leg cramps, nausea, dizziness, risk of osteosarcoma development
Use for up to 2 years	\$30 / dose		
Bolus subcutaneous injection into thigh or abdomen	Patent Expires in 2018		Other Notes: Zelos Therapeutics has a nasal spray in early stages of clinical trials (NDA planned for 2012). Patch formulation undergoing phase II trials outside of the US
Mol. mass 4117.72 g/mol	Formula C181H291N55O51S2		
Pros	Cons	Recommendation	
Small dosage Taken daily Taken up to 2 years Market predicted to achieve blockbuster status (\$2billion) by 2018	Bolus subcutaneous administration 2 competing delivery methods in trials	Very promising drug with the lowest dosage, a large and growing market, and predicted platform compatibility due to molecule's similarity to insulin.	

Table 12, summary of Terparatide investigation ^[23]

Teriparatide is the portion of human parathyroid hormone (PTH), amino acid sequence 1 through 34, of the complete molecule (containing 84 amino acids). Endogenous PTH

is the primary regulator of calcium and phosphate metabolism in bone and kidney. PTH increases serum calcium, partially accomplishing this by increasing bone resorption. Thus, chronically elevated PTH will deplete bone stores. However, intermittent exposure to PTH will activate osteoblasts more than osteoclasts. Thus, once-daily injections of Teriparatide have a net effect of stimulating new bone formation leading to increased bone mineral density ^[23].

Teriparatide is the first, and to date only, FDA approved agent for the treatment of osteoporosis that stimulates new bone formation ^[23].

Concluding Remarks

The buccal antibiotic delivery offers clinician and health care insurers an effective alternative to reduce hospital associated infections. Furthermore, the high patient compliance rate, the increasing need of the clinical and market community for antimicrobials, the physiological advantages of the buccal tissue and GI track and IV drug delivery limitations, create beneficial conditions for delivering certain broad spectrum antibiotics via the buccal patch [7, 8, 10, 11].

The properties of the buccal mucosa make it well positioned for controlled drug delivery over extended periods of time. Such properties include the highly vascular buccal mucosa membrane as well as avoidance of GI track's harsh environment and the first-pass metabolism. This area is well suited for a retentive device that patients appear to accept well [2, 7, 8].

Research shows that the mucosa's local environment and permeability can be controlled and manipulated with proper formulation and dosing. This makes buccal drug delivery an attractive alternative for systemic delivery especially compared to the inefficient oral delivery. Exploring and discovering safe and effective permeation/absorption enhancers is crucial to the future of buccal drug delivery. Continued research is essential to making this alternative drug delivery technique completely achievable in the near future [2,7, 8].

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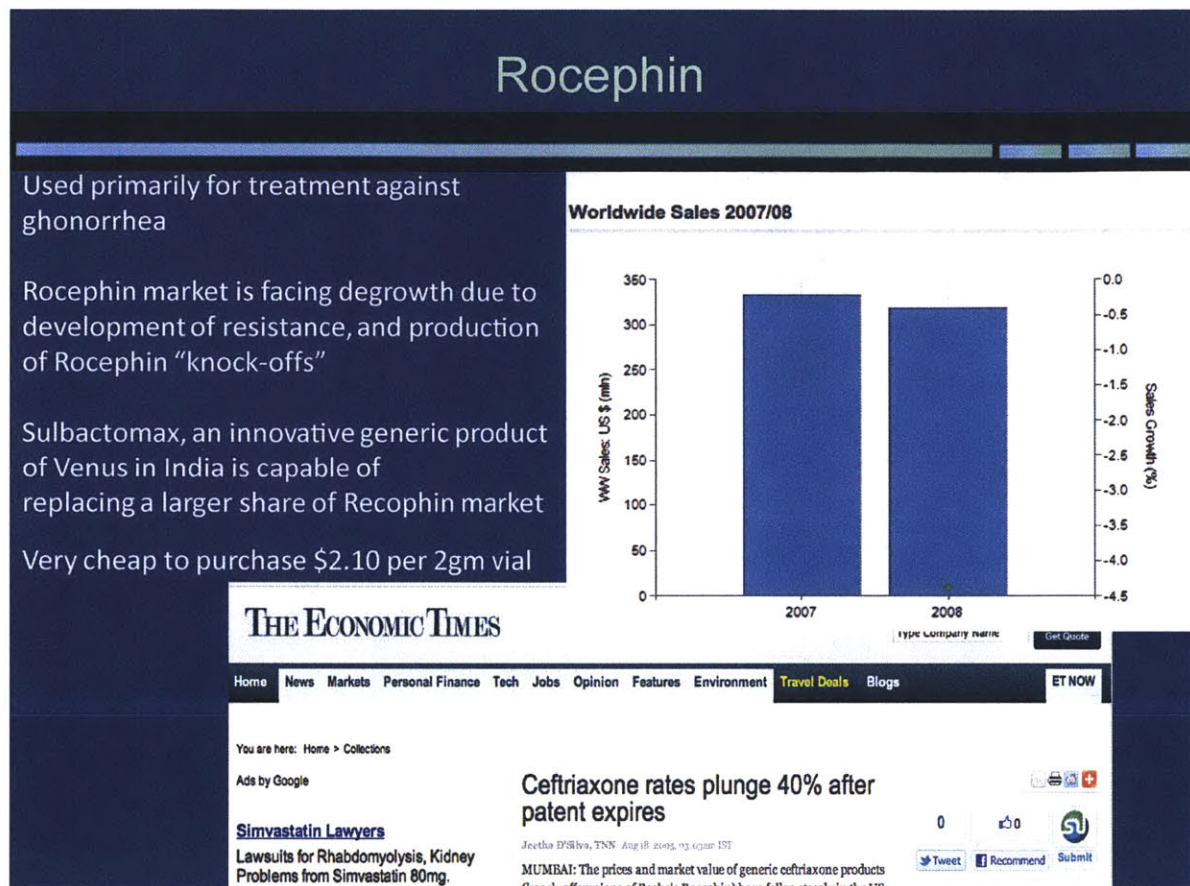
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Appendices

Appendix A: Interviews

Name (Last, First)	Title	Company
Fleming, Jonathan	Partner, Founder	Oxford Bio Sciences
Navia, Manuel	Drug Discovery and Development Advisor	Oxford Bio Sciences
Bukuras, Mark	Account Manager	Novartis
Roberts, Dave	Director, External Business Operations, Technical R&D	Novartis
Zion, Todd	CEO	Smart Cells
de los Pinos, Elisabet	CEO	Aura Biosciences
Benny, Ofra	Associate Professor of Surgery	Harvard Medical School
Warren, Shaw	MD	Mass General Hospital
Walker, Bruce	MD	Mass General Hospital
Chari, Raghav	PhD	Dr. Reddy's Laboratories
Zarur, Andrey	VC Partner, Lecturer @ Sloan, MIT	Kodiak Venture Partners

Appendix B: Sample Research



Appendix C: Research Conclusion

Drug	Terparatide (Forteo)	Daptomycin	Cancidas	Enfuvirtide (Fuzeon)	Gentamycin	Ceptaz	Rocephin	Colistimethate	Doripenem
Min. dose (in mg)	0.02	4-6mg/kg	50	90	100	250	250	250	250
Doses per day	1	1	1	2	1 - 3	2 to 3	1 to 2	2 - 4	3
Bolus or Basal administration	Bolus	basal and bolus	basal	Bolus	both	bolus	Bolus	basal	Basal
If basal, what is a common/ acceptable duration		30mins	1		2 hours	N/A		It may be injected into a vein over 3 to 5 minutes or mixed in a solution and given slowly into a vein over 22 to 23 hours.	1 hour
Molecular weight	4117.72 g/mol	1619.7086 g/mol	1213.4	4492 g/mol	477.6	636.6	661.59 g/mol	1155 g/mol	420.5
Compound Formula	C181H291N55O51S2	C72H101N17O26	C52H88N10O15	C202H298N50O64	C21H43N5O7	C22H32N6O12S2	C18H16N8Na2O7S3•3.5H2O	C58H105N16Na5O28S5	C15H24N4O6S2

Appendix D: Example of Market Analysis

Gentamycin - aminoglycoside antibiotic

- 1) Synonyms: Gentamycin, Garamycin, Gentiomycin C
- 2) Doses per day: 1-3, depending on condition. 3-7 mg/kg/day
- 3) Both bolus and basal administration (basal duration - up to two hours)
- 4) Molecular Formula and Weight:
 1. Molecular Formula:
 1. Gentamicin C 1 : C 21 H 43 N 5 O 7
 2. Gentamicin C 2 : C 20 H 41 N 5 O 7
 3. Gentamicin C 1a : C 19 H 39 N 5 O 7
 2. Molecular Weight (free base) :
 1. Gentamicin C 1 = 477.6
 2. Gentamicin C 2 = 463.6
 3. Gentamicin C 1a = 449.5
- 5) Toxic and other side effects: yes, nephrotoxic. Blood levels must be monitored.
Loss of hearing, balance, and vision due to vestibular apparatus damage.
- 6) Price: \$0.12/mg
- 7) Patient type: all, mostly adult
- 8) Most common uses: gram-negative infections (see more info)
- 9) Patent: originally Abbot Labs, 1977.

(Wikipedia)

- not given orally due to low absorption from small intestine
- Gentamicin can also be highly nephrotoxic, particularly if multiple doses accumulate over a course of treatment.
 - For this reason gentamicin is usually dosed by body weight.
 - Also trough and peak serum levels of gentamicin are monitored during treatment, generally before and after the third dose is infused.

(Merck Manual)

- Labeled Indications
 - susceptible bacterial infections, normally gram-negative organisms,
 - *Pseudomonas*,
 - *Proteus*,
 - *Serratia*,
 - gram-positive *Staphylococcus*;
 - treatment of bone infections,
 - respiratory tract infections,
 - skin and soft tissue infections,
 - abdominal and urinary tract infections,
 - septicemia;
- Dosage, Adults:
 - I.M., I.V.:
 - Conventional: 1-2.5 mg/kg/dose every 8-12 hours
 - Once daily: 4-7 mg/kg/dose once daily; some clinicians recommend this approach for all patients with normal renal function; this dose is

at least as efficacious with similar, if not less, toxicity than conventional dosing

- **Brucellosis (100 cases/year):** 240 mg (I.M.) daily or 5 mg/kg (I.V.) daily for 7 days; either regimen recommended in combination with doxycycline
- **Cholangitis (Increasing. In 2000, 20.9 per 100,000 men, 6.3 per 100,000 women):** 4-6 mg/kg once daily with ampicillin
- **Diverticulitis – complicated (312,000 admissions and 1.5 million days of inpatient care per year):** 1.5-2 mg/kg every 8 hours (with ampicillin and metronidazole)
- **Endocarditis (10000 to 15000 new cases/year):** Treatment: 3 mg/kg/day in 1-3 divided doses
- **Meningitis (rare):**
 - *Enterococcus* sp or *Pseudomonas aeruginosa*: Loading dose 2 mg/kg, then 1.7 mg/kg/dose every 8 hours (administered with another bacteriocidal drug)
 - *Listeria*: 5-7 mg/kg/day (with penicillin) for 1 week
- **Pelvic inflammatory disease (750,000 cases/year):** Loading dose: 2 mg/kg, then 1.5 mg/kg every 8 hours
- **Plague (10-15 cases/year):** Treatment: 5 mg/kg/day, followed by postexposure prophylaxis with doxycycline
- **Pneumonia, hospital- or ventilator-associated (300,000 cases/year):** 7 mg/kg/day (with antipseudomonal beta-lactam or carbapenem)

- **Synergy (for gram-positive infections) – numbers difficult to find:** 3 mg/kg/day in 1-3 divided doses (with ampicillin)
- **Tularemia (<1/1,000,000 people/year):** 5 mg/kg/day divided every 8 hours for 1-2 weeks
- **Urinary tract infection (8-10 million, but gentamicin used only in most serious cases):** 1.5 mg/kg/dose every 8 hours

disease		mg/kg/day	mg/kg/day/year
Brucellosis	100	5	500
Cholangitis**	38080	5	190,400
Diverticulitis	312,000	6	1,872,000
Endocarditis	12500	3	37,500
PID	750,000	4.5	3,375,000
Plague	12	5	60
Pneumonia	300,000	7	2,100,000
		TOTAL	7,575,460
			mg/kg/day of treatment

* Not including synergy, UTI, or meningitis due to lack of good numbers

** based on 140 million men and 140 million women in US

Average Weight in US = 80 kg

Total	606,036,800	mg/day treatment	of
-------	-------------	---------------------	----

Cost = \$.12/mg

Total	72,724,416	\$/day of treatment
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Average time of treatment = 4.5 days

Total	\$327,259,872	year
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Note that this assumes all disease cases will be treated with gentamicin, which is obviously unlikely to be true.

Appendix E: Example of Clinical interviews

Interview with “Boston Home Infusions” - first on the phone and then by email.

The minutes from our phone conversation are as follows:

- Jessica said that their nurses don't actually administer the drugs - the patients do it themselves! The nurses teach them how to do it while they're in the hospital and then once they're discharged, the nurses visit weekly to check up.
- In the hospital, the nurses insert a "peripherally inserted central catheter" into the inner elbow of the patient. The patient is totally active with this line in - not bed ridden at all. When pressed, she said the patients cannot lift anything >5lbs with the line in and that sometimes rashes develop, etc.
- Some drugs require weekly blood levels to be drawn to determine whether to adjust the dosage. She didn't really like my question about whether the dosage range had to be narrow or whether it could allow for variation but it seems like the drugs that don't require these weekly blood level checks have more of a give re: dosage.
- The IV antibiotics they 'administer' most commonly are as follows:
 1. **Cancomycin** which is used to treat infections (such as MRSA). Treatment can last anywhere between 7 days to 3 months. Dosage has to be accurate because weekly blood levels are drawn and dosage adjusted accordingly.
 2. **Ceftriaxone** also for infections. Similar info as above.

Total Parenteral Nutrition used for mal-absorption in GI tract. This can be administered from 1 week to lifetime! Dosage is not quite as important. When I looked this up afterward, it looks like this is just IV food not antibiotic.

I asked her about some of our top candidates and the good news is they do see patients on a weekly basis for most of them! I quickly jotted the info in the columns to the right of assigned market researcher on the Google doc. The top three drugs listed above are used for ~100 patients per week.

- I asked whether she thought the patients would benefit from an antibiotic gum. She seemed surprised by the idea, so I mentioned insulin chewing gum (since there are other companies producing that already too). She became skeptical because she thought the gum mechanism was oral, but I decided not to correct her and just moved on. In theory, she said, the patients would definitely be into gum.
- When I asked about bolus vs. gradual injection she said there are several infusion methods in use: elastomeric device, cadd pump, and something else I couldn't understand (some sort of tubing). They almost always use the elastomeric device. (<http://www.ncbi.nlm.nih.gov/pubmed/1621729>) I think the rate is 100mL per hour? She said it's definitely not bolus; it goes gradually and patients do it daily.

She didn't have any idea how much it costs for nurse visits because she's in the pharmacy department. I later emailed her specific questions about our 6 finalist candidate drugs and she responded as follows:

1. Approximately how many patients do you administer this drug to on a weekly basis?

Cancidas - 2-3 pts weekly

Enfuviritide - 0

Tygacil - 2-4 pts

Doripenem - 0-1 pts

Targocid - 0

Ceptaz - If this is Ceftazidime 5-6 pts

2. What is the duration of treatment? And the frequency of patient administration?

Cancidas - daily admin, up to 6 weeks

Enfuviritide - -

Tygacil - twice daily for 2-4 weeks

Doripenem - three times daily for 2 weeks

Targocid - -

Ceptaz - usually three times daily (can be twice daily) for 2-4 weeks

3. Do you check blood levels weekly? What is the range of drug present in blood that is acceptable before you have to change the patient's dosage?

Cancidas - no drug level monitoring done

Enfuviritide - -

Tygacil - no drug level monitoring done

Doripenem -no drug level monitoring done

Targocid - -

Ceptaz -no drug level monitoring done

4. Do you see skin irritation from the drug (not just the catheter) near area of administration?

Nothing stands out in particular on any of these drugs in terms of skin irritation solely related to the drug. Cancidas - Enfuvirtide - Tygacil - Doripenem -Targocid -Ceptaz –

5. What are the main indications for this drug? Is it often taken in concurrence with something else?

Cancidas - fungal infection, administered alone

Enfuvirtide - HIV, yes

Tygacil - skin infections/pneumonia, administered alone

Doripenem - abd infections/pneumonia, administration

Targocid - not currently used here in the US

Ceptaz - skin/bone/abdominal infections, used alone pneumonia, may be used with another drug

6. Do you use the brand name or generic?

Cancidas - Brand

Enfuvirtide - -

Tygacil - Brand

Doripenem - Brand

Targocid - -

Ceptaz - Generic

Appendix F: Examples of some analysis

	A	B	C	D	E	F	G	H
1	Drug	Min. dose (mg)	Doses per day	Bolus or Basal?	If basal, what is a common duration?	Molecular weight	Compound Formula	Toxic and other side effects
2	Terparatide (Forteo)	0.02	1	Bolus		4117.72 g/mol	C181H291N55O51S2	Increased risk of osteosarcoma, nausea, leg cramps and dizziness
3	Candidas	50	1	basal	1	1213.4	C52H88N10O15	some hepatic effects
4	Tygacil	50	100 mg, then 50 mg/12 hours	basal	30 to 60 mins	585.65 g/mol	C29H39N5O8	Diarrhea, nausea and vomiting; Pain at the injection site, swelling and irritation; increased or decreased heart rate and infections.
5	Enfuvirtide (Fuzeon)	90	2	Bolus		4492 g/mol	C202H298N50O64	Injection site reactions, peripheral neuropathy, insomnia, depression, cough, dyspnoea, anorexia, arthralgia, infections and/or eosinophilia.
6	Gentamycin	100	1 to 3	both	2 hours	477.6	C21H43N5O7	nephrotoxic, blood levels must be checked. Possible vestibular apparatus damage
7	Targocid (Teicoplanin)	200	1	both	30 min	1564.3 to 1907.7	C77H77N9O31Cl2.R (variable)	dizziness and headaches, skin rash
8	Cephazolin	250						
9	Ceptaz	250	2 to 3	bolus	N/A	636.6	C22H32N6O12S2	phlebitis, inflammation, pruritus, rash, fever, diarrhea, vomiting, abdominal pain, pseudomembranous colitis, headache, dizziness, paresthesia, cadidiasis, vaginitis, hemolytic anemia
10	Rocephin	250	1 to 2	Bolus		661.59 g/mol	C18H16N8Na2O7S3*3.5H2O	Pain and swelling at injection site, diarrhea, increase in liver enzymes, hives, bloody stool, rash, itching, wheezing
11	Colistimethate	250	2 to 4	basal	22 to 23 hours	1155 g/mol	C58H105N16Na5O28S5	diarrhea, fever, vomiting, muscle weakness, trouble breathing, allergic reactions
12	Doripenem	250	3	Basal	1 hour	420.5	C15H24N4O6S2	Anaphylaxis, sodium valproate, clostridium difficile-associated diarrhea, development of drug-resistant bacteria, pneumonitis with inhalational use
13	Imipenem	250	8	basal	20-30 min	299.347 g/mol	C12H17N3O4S	Nausea and vomiting
14	Kanamycin	250	2	both	30-60 min	484.5g/mol	C18h38n4o1	Serious side effects include tinnitus or loss of hearing, toxicity to kidneys, and allergic reactions to the drug.
15	Lactobionate	250						
16	Oxacillin	250	4 to 6	Both		401g/mol	C19H19N3O5S	Neurotoxic reactions, Renal tubular damage and interstitial nephritis, Pseudomembranous colitis, Hepatotoxicity, characterized by fever, nausea, and vomiting
17	Daptomycin	320	1	basal and bolus	30mins	1619.7086 g/mol	C72H101N17O26	

Appendix G: A PK/PD Approach to Antibiotic Therapy

From rxkinetics.com

http://www.rxkinetics.com/antibiotic_pk_pd.html

Introduction

Pharmacokinetics (PK) is concerned with the time course of antimicrobial concentrations in the body, while Pharmacodynamics (PD) is concerned with the relationship between those concentrations and the antimicrobial effect. Antibiotic dosing regimens have traditionally been determined by PK parameters only. However, PD plays an equal, if not more important, role. In this age of increasing antimicrobial resistance, PD becomes even more important because these parameters may be used to design dosing regimens which counteract or prevent resistance.

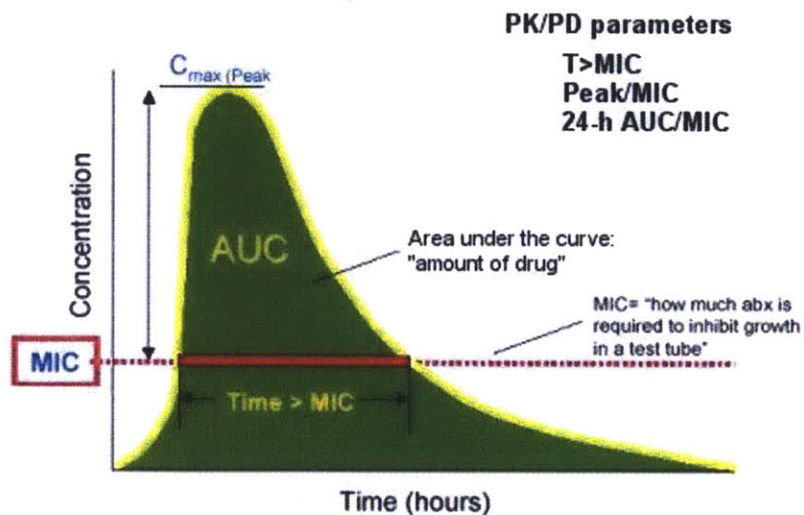
Discussion

The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro. While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity.

PK parameters quantify the serum level time course of an antibiotic. The three pharmacokinetic parameters that are most important for evaluating antibiotic efficacy are the peak serum level (C_{max}), the trough level (C_{min}), and the Area Under the serum concentration time Curve (AUC). While these parameters quantify the serum level time course, they do not describe the killing activity of an antibiotic.

Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic: the Peak/MIC ratio, the $T > MIC$, and the 24h-AUC/MIC ratio. The Peak/MIC ratio is simply the C_{pmax} divided by the MIC. The $T > MIC$ (time above MIC) is the percentage of a dosage interval in which the serum level exceeds the MIC. The 24h-AUC/MIC ratio is determined by dividing the 24-hour-AUC by the MIC.

Pharmacokinetic/Pharmacodynamic Predictors of Efficacy



Antimicrobial Patterns

The three Pharmacodynamics properties of antibiotics that best describe killing activity are time-dependence, concentration-dependence, and persistent effects. The rate of killing is determined by either the length of time necessary to kill (time-dependent), or the effect of increasing concentrations (concentration-dependent). Persistent effects include the Post-Antibiotic Effect (PAE). PAE is the persistent suppression of bacterial growth following antibiotic exposure.

Using these parameters, antibiotics can be divided into 3 categories:

Pattern of Activity	Antibiotics	Goal of Therapy	PK/PD Parameter
Type I Concentration-dependent killing and Prolonged persistent effects	Aminoglycosides Daptomycin Fluoroquinolones Ketolides	Maximize concentrations	$24h-AUC/MIC$ $Peak/MIC$
Type II	Carbapenems	Maximize duration of	$T > MIC$

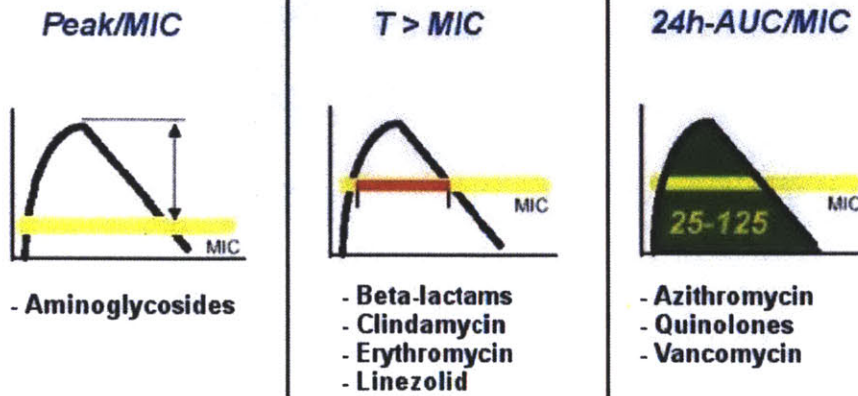
Time-dependent killing and Minimal persistent effects	Cephalosporins Erythromycin Linezolid Penicillins	exposure	
Type III Time-dependent killing and Moderate to prolonged persistent effects.	Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin	Maximize amount of drug	24h-AUC/MIC

For **Type I** antibiotics (AG's, fluoroquinolones, daptomycin and the ketolides), the ideal dosing regimen would maximize **concentration**, because the higher the concentration, the more extensive and the faster is the degree of killing. Therefore, the 24h-AUC/MIC ratio, and the Peak/MIC ratio are important predictors of antibiotic efficacy. For amino glycosides, it is best to have a Peak/MIC ratio of at least 8-10 to prevent resistance. For Fluoroquinolone vs gram negative bacteria, the optimal 24h-AUC/MIC ratio is approximately 125. Versus gram positives, 40 appears to be optimal. However, the ideal 24h-AUC/MIC ratio for FQ's varies widely in the literature.

Type II antibiotics (beta-Lactams, clindamycin, erythromycin, and linezolid) demonstrate the complete opposite properties. The ideal dosing regimen for these antibiotics maximizes the **duration** of exposure. The T>MIC is the parameter that best correlates with efficacy. For beta-Lactams and erythromycin, maximum killing is seen when the time above MIC is at least 70% of the dosing interval.

Type III antibiotics (vancomycin, tetracycline's, azithromycin, and the dalfoprstin-quinupristin combination) have mixed properties; they have time-dependent killing and moderate persistent effects. The ideal dosing regimen for these antibiotics maximizes the **amount** of drug received. Therefore, the 24h-AUC/MIC ratio is the parameter that correlates with efficacy. For vancomycin, a 24h-AUC/MIC ratio of at least 125 is necessary (some researchers recommend a ratio of 400 or more for problem bugs).

Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Profiles



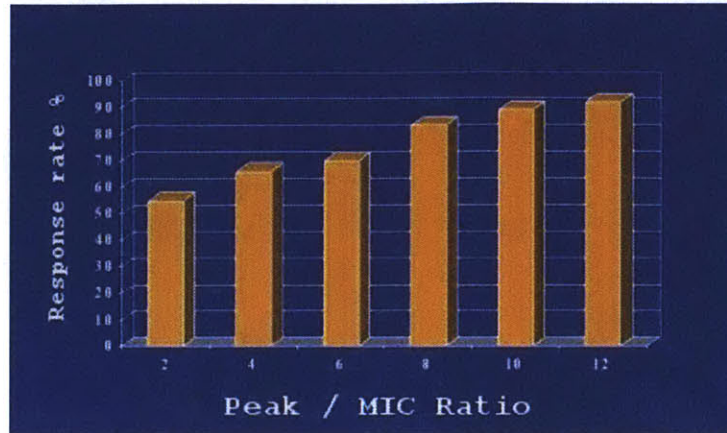
Outcome studies

Aminoglycoside Pharmacodynamics in Vivo

Initial serum peak level	Died	Survived
< 5mcg/ml	21%	79%
≥ 5 mcg/ml	2%	98%

Moore et al, J Infect Dis 149: 443, 1984

Aminoglycoside Pharmacodynamics in vivo



Moore et al, J Infect Dis 155: 93, 1987

Vancomycin Outcome vs 24h-AUC/MIC ratio

24h-AUC/MIC ratio	Satisfactory	Unsatisfactory
< 125	4 (50%)	4
> 125	71 (97%)	2

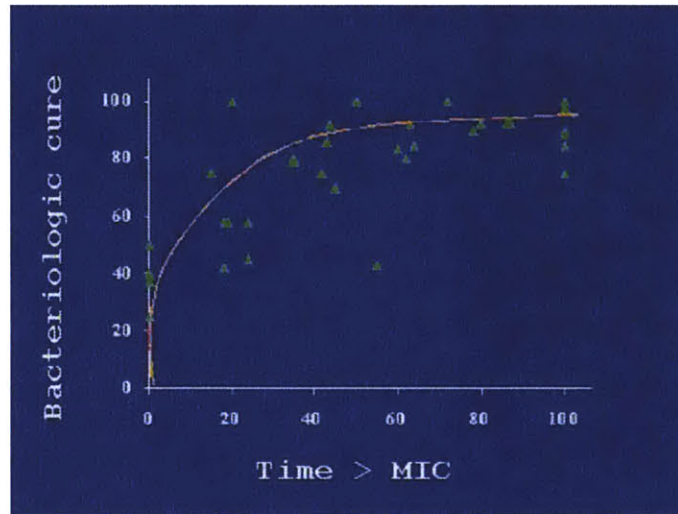
Hyatt et al, Clin Pharmacokinetic 28: 143, 1995

Fluoroquinolone Pharmacodynamics vs *S. pneumonia*

24h-AUC/MIC ratio	Microbiological Response
< 33.7	(64%)
> 33.7	(100%)

Ambrose et al, Antimicrob Agents Chemo 10: 2793, 2001

Pharmacodynamics of Beta-Lactams and Macrolides in Otitis Media



Craig et al, Ped Infect Dis 15: 255, 1996

Conclusion

PK dosing has shown us that one dose is not appropriate for all patients. Pharmacodynamics shows us that one target level is not appropriate for all patients. We need to evaluate both the serum level data and the MIC, taking into consideration the PD properties of the drug.

Numerous outcome studies have shown that class-appropriate PK/PD parameters are excellent predictors of antibiotic efficacy.

Appendix H: Examples of Interviews with Industry leaders and Venture Capital Firm

Interview with Dr. Navia, Oxford Biosciences

Finding the Best Drug Candidates for Buccal Delivery

The following is the brief description for Privo's market needs:

- 1) Look into several different drug classes such as antibiotics, hormones (growth,...), cancer drugs, vaccines and HIV.
- 2) Find out from clinical experts in each field, what the ideal candidates drugs are for Privo's platform technology (endocrinologist for diabetes and hormones, infectious disease for antibiotics,...)
- 3) Examples could be FUZEON (enfuvirtide) for HIV, Insulin for diabetes, growth hormone, polio for vaccines and
- 4) See which drugs within each class has the following principle requirements:
 - a. Replacing injection for buccal delivery would be a great benefit to the patient
 - b. Big market demand, get the market size
 - c. What would appropriate prices
 - d. Could reduce the cost of "Step Down": in-between hospital to home transition
 - e. Find out the Risk/Benefit ratio
 - f. Find out the patient compliance benefits
 - g. Find out the dosage for each drug

- h. We can then figure out if we can fit the required dose in the gum or lozenges

Minutes of meeting with Dr. Martyn Botfield

Aug 09, 2010, lunch meeting at 4 burgers, Cambridge, Ma

Attendees: Martyn Botfield, Manijeh Goldberg, arranged via Beth Edwards (my mentor at Vertex)

Martyn Botfield, PhD

Senior Director & Global Head, Biomarker Research & Translational Pharmacology

Vertex Pharmaceuticals, 130 Waverly St, Cambridge MA 02136, 617.444.6375 (office)

Martyn received his PHD in BioChemistry from Harvard and has been a professor at Harvard medical School teaching HST students.

- 1) Martyn was concerned that mucosa drug delivery is a poisoned well because of Pfizer's Exubera
- 2) He said that making a safe and acceptable bio-available solution for insulin and other drugs is not a trivial job and anyone dealing with pharma understands the complexity of it.
- 3) The FDA will not directly talk to you and give you advice because of regulations
- 4) The FDA will only comment if you have written them a proposal and they will say what things they do not approve, but will not give you reasons in most cases.
- 5) Usually you can ask questions from FDA consultants

- 6) He said he will try to contact some one that might help with contacting Eli Lilly
- 7) He said look into Orasure a company for oral HIV test
- 8) Martyn suggested creating a charitable cause for doing oral drug delivery, insulin
- 9) Martyn said that I can call him and ask any questions or just give him updates on a regular basis
- 10) See if you can make a HCV test for Marines with the chewing gum
- 11) Make a collection Chewing gum and not just a delivery gum:
 - a. This can be a once a month gum indicating metabolic disorders, proteins,...
 - b. Defense department will be very interested in this
 - c. Talk to a VA hospital about their needs
 - d. Collects saliva and DNA
 - e. Having the DNA ensures that the user cannot cheat and use someone else's gum
 - f. Could Indicate any usage of addictive substances
 - g. Could Indicate Hepatitis C virus
 - h. Could Indicate other type of war related diseases
 - i. Could Indicate Post Traumatic Syndrome
 - j. Could indicate any other toxins in the air/water that the soldiers are exposed to.
 - k. See if you can make a gum that can sustain the content, proteins, saliva, bacteria and soon, put the gum in a specific container and ship it to a lab